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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Maes, et al.

Serial No.: 09/773,351 Group Art Unit: 1617

Filed: January 31, 2001 Examiner: Jiang, Shaojia A.

For: Cholesterol Sulfate and Amino Sugar Compositions for Enhancement of Stratum Corneum Function

REMARKS

The Examiner previously rejected Claims 1 and 3 to 20 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-21 of copending Application No. 10/424,616. The claims of the copending Application are believed to be still pending. Applicants acknowledge the provisional double patent rejection made by the Examiner. However, in light of the arguments set forth below, Applicants will make a terminal disclaimer, if necessary, in the event that allowable subject matter is indicated.

A. The Present Invention is Novel Over U.S. Patent No. 5,650,166 ("the '166 Ribier reference")

In the present office action, the Examiner responds to Applicants arguments that the arrangement of the components in the '166 Ribier reference are not as a mixture, and therefore, the '166 Ribier reference fails to disclose an element of the present claims. Anticipation requires identity of invention: the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1267, 20 USPQ2d 1746, 1748 (Fed. Cir. 1991). *See also In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it"). Therefore, Applicants assert that it is relevant whether features set forth in the present claims are present in the cited reference. This is because the present invention is based on the arrangement of the ingredients. That the elements in the '166 Ribier reference are not arranged as they are in the present invention has not been addressed.

The arrangement in the '166 Ribier reference is not a "mixture" as one of ordinary skill in the art would understand it. Two ingredients that are separated from one another, as they are in the '166 Ribier by virtue of the vesicle formation, cannot be a mixture or be integral with one another because they are not actually combined. The Examiner has admitted in the present office action that a mixture can be interpreted by one of ordinary skill in the art as being integral with. Therefore, Applicants assert that the

claims are limited in a way that one of ordinary skill in the art would understand that the present invention is a mixture separate and distinct from the separate lipid bilayers of the '166 Ribier reference. There is no integration where there is separation. Therefore, the '166 Ribier reference does not anticipate the claims of the present invention because it fails to disclose a mixture or, in other words, integral with. In deciding the issue of anticipation, two steps must be taken: first, the elements of the claims must be identified to determine their meaning in light of the specification; and second, the corresponding elements disclosed in the allegedly anticipating reference must be identified. *Lindemann Maschinenfabrik GMBG v. Am. Hoist and Derrick Co. et al.*, 221 USPQ 481, 485; *Cf. Slimfold Mfg. Co. v. Kinkead Indus., Inc.*, 810 F.2d 1113, 1116, 1 USPQ2d 1563, 1566 (Fed. Cir. 1987). As the second step has not been taken and cannot be taken because a mixture is not found in the '166 Ribier reference, Applicants request that the rejection of the claims based on anticipation be withdrawn.

B. The Present Invention is Non-obvious in View of the Cited References

1. The '166 Ribier Reference

The Examiner notes in the final office action that notwithstanding the fact that the '166 Ribier reference fails to disclose the amount of each of the ingredient components of the present invention, one of ordinary skill in the art would know to use the amounts of the ingredients taught in the '166 Ribier reference. Therefore, according to the Examiner Claims 13 to 20 of the present invention are obvious. Applicants respectfully traverse this line of reasoning because the '166 Ribier reference, as discussed above with respect to the novelty rejection, fails to teach or suggest a mixture of the ingredients such that they are integral with one another.

The limitations of the claims sufficiently describe an integral mixture of components which one of ordinary skill in the art would recognize as being distinct and separate from the same components physically located in separate bilayers of a liposome (or vesicle) as they are in the '166 Ribier reference. Applicants have not found that this point has been addressed. "A proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out [the claimed process], those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 20 USPQ2d 1438, 1442 (CAFC 1991); see *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). These two factors have not been met in the present case. First, there is no teaching or suggestion in the prior to make a mixture of the pertinent components in the '166 Ribier reference. The teaching in the '166 Ribier reference of the components physically located in separate bilayers of a liposome is

contrary and opposite to the mixture of the same components of the present invention. In a mixture, the components are not separated; but rather, are integrated. Since the '166 Ribier reference only teaches the components in a state of separation, the mixture of the present invention is not taught or suggested by the '166 Ribier reference.

The second factor of an obviousness analysis is likewise not met because the '166 Ribier reference fails to reveal that making the composition of the present invention, namely the mixture of the components, would be expected by one of ordinary skill in the art to have reasonable success. This factor is linked to the first factor because as long as there is no teaching or suggestion in the '166 Ribier reference to make the mixture of the present invention, there likewise, cannot be a reasonable expectation of success to do what is not taught or suggested. But beyond this, the teachings of the '166 Ribier reference are aimed at treating two different layers of the skin at the same time. Thus, the components of the '166 Ribier compositions start out separated in the composition and the components remain separated as they are directed to two different areas of the skin. There is never a mixing or integration of the components of the '166 Ribier compositions. This is illustrated by the teaching at column 1, lines 11 to 14, where the '166 Ribier compositions are described as comprising at least one active agent conveyed via at least two distinct types of lipid vesicles. Additional support is found at column 2, lines 19 to 21, of the '166 Ribier reference wherein it is taught that the alleged invention involves two different agents to act in different areas of the skin. The different agents act in different areas due to the different lipid vesicles containing them. The different vesicles are classified based on the different types of action (see column 2, lines 34 to 41.) Every aspect of the '166 Ribier compositions relates to being separate and distinct. Thus, the '166 Ribier reference does not teach, suggest, nor motivate one of ordinary skill in the art to make the compositions of the present invention having mixed components. Accordingly, the present invention is not obvious in view of the '166 Ribier reference and Applicants request that this rejection be withdrawn.

2. U.S. Patent Nos. 5,925,364 and 5,411,742

In the final office action, the Examiner states Applicants assertion and asserts that the present claims are not limited to the act of mixing to produce a mixture and in what orderly manner to form discrete layers of a vesicle dispersed in the aqueous phase. It is not clear what is intended by the latter part of this assertion. As the Examiner noted, Applicants assert that the act of mixing can produce two different results, namely, one being a mixture and the other being a vesicle with discrete layers. The process is irrelevant. What is at issue in the present application is that the results of mixing are different, and that the claims are directed to features that are not present in vesicle. The Examiner maintains the

rejection of Claims 1 and 3 to 20 because both cited references, U.S. Patent Nos. 5,925,364 ("the '364 reference") and 5,411,742 ("the '742 reference"), teach an integral mixture in a stabilized oil-in-water emulsion without discrete layers of a lipid vesicle.

Applicants pointed out in their last response that the cited references teach that discrete layers of a lipid vesicle are formed by mixing. If an inventor takes steps that the prior art suggests cannot be made, it is probative of non-obviousness. *Yamanouchi Pharm. Co. v. Danbury Pharmacal Inc.*, 21 F. Supp. 2d 366, 374 n. 15, 48 USPQ2d 1741, 1748 n. 15 (S.D. N.Y. 1998), *aff'd*, 231 F.3d 1339, 56 USPQ2d 1641 (Fed. Cir. 2000). Thus, based on the cited references, one of ordinary skill in the art would expect to make vesicles with discrete layers by mixing and not the mixture of the present invention. Because the result of the present invention is different than the result taught by the cited references, the claims are adequately directed to limitations that distinguish these results. It is not permissible to pick and choose only so much of any given reference as will support a given position and ignore the reference in its totality." *Lubrizol Corp. V. Exxon Corp.*, 986 F. supp. 302, 322, 7 USPQ2d 1513, 1527 (N.D. Ohio 1988). Specifically, it is indicated in the '742 reference at column 1, lines 38 to 54, that ionic lipids are capable of swelling in an aqueous solution to form a lamellar phase, and after stirring, to form vesicles dispersed in the aqueous solution. The '364 preparation does not produce a mixture because the ionic lipids swell under the action of mixing to form discrete layers of a lipid vesicle which separates its contents from the other ingredients in the composition, namely the outside media (e.g., the aqueous phase). Therefore, there is no teaching or suggestion of a mixture like that of the present invention in these cited references.

As previously discussed in Applicants last response, none of the cited references teaches or suggests that the act of mixing produces a mixture. To the contrary, the act of mixing in the cited references causes the ionic lipid to swell and arrange itself in an orderly manner to form discrete layers of a vesicle dispersed in the aqueous phase. Thus, the ionic lipid used with other materials to make the vesicle is not mixed with the content of the aqueous phase; but, rather is used to form a discrete entities present in the outside media (i.e., the aqueous phase). They are not mixed as an end product. As previously discussed, the vesicle holds active agents within and keeps the actives separate from media outside of its walls. Creating a vesicle is akin to encapsulation where the actives inside and the materials used to encapsulate are not mixed with the outside media. Therefore, the combination of the '364 Ribier reference and the '742 reference fails to teach or suggest the mixture of the present invention.

3. U.S. Patent Nos. 5,650,166, 6,150,381, and 5,702,691

According to the Examiner, the '166 Ribier reference in combination with the '381 reference and in further view of U.S. Patent No. 5,702,691 issued to Ichinose et al. ("the '691 reference") renders Claims 10 to 12 and 20 obvious. In acknowledging Applicants remarks in their last response regarding the '166 reference, the Examiner notes that the present claims are not limited to a particular form of a mixture. However, Applicants assert that the present claims are in fact limited to a mixture wherein the ingredients are integral with one another. Specifically, Claim 1 of the present invention, as amended, states the following.

> A composition for topical application to the skin comprising a mixture of effective amounts of cholesterol sulfate or salts thereof present in an amount between 0.05 to about 5.00 percent, integral with an exfoliant present in an amount between 0.1 to about 10.0 percent in a cosmetically or pharmaceutically acceptable vehicle.

Thus, the present claims as previously amended specify that the mixture is one where cholesterol sulfate in certain amounts is integral with an exfoliant in certain amounts. This is not taught or suggested by any of the cited references, and no further limitations seem to be necessary to distinguish the present invention from the cited references.

The '381 reference teaches sclareolide-like compounds for treating disorders caused by microbials such as, for example, bacteria, and one specific disorder is acne. As disclosed in the '381 reference, topical formulations containing sclareolide are generally prepared by admixing sclareolide in water and at least one organic solvent. However, this does not remedy the defect of the '166 reference. Since the '166 reference teaches lipid vesicles encapsulating water soluble actives, the combination of these references at most suggests that sclareolide could be incorporated within the aqueous phase of the '166 lipid vesicles (i.e., sclareolide could be encapsulated). Because lipid vesicles are not simple admixtures, the combination of the '166 reference and the '381 reference fails to teach or suggest the compositions of the present invention. Finally, the '691 reference teaches flavanonol derivatives in hair nourishing and hair growth products and is cited by the Examiner for its teaching of the anti-inflammatory properties of white birch extract. However, like that of the '381 reference, the teachings of the '691 reference do nothing to remedy the defect of the '166 reference. Essentially, none of the cited references alone or in combination teach or suggest a mixture of cholesterol sulfate and an exfoliant such that the two are integral with one another as an end product. In order to make out a *prima facie* case of obviousness, it must be shown that there is a suggestion to one of ordinary skill in the art to make the combination of cited references or a teaching to one skilled in the art of a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Finally, Applicants point out that the burden to provide evidence of unexpected results does not pass from the Examiner to Applicants until a *prima facie* case of obviousness has been made. In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Rijckaert*, 28 USPQ2d 1955, 1956 (CAFC 1993) (citing *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant. *Id.* "A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." *Id.*, (citing *In re Bell* , 991 F.2d 781, 782, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993) (quoting *In re Rinehart*, 531 F.2d 1048, 1051, 189 USPQ 143, 147 (CCPA 1976)). Since a *prima facie* case of obviousness has not been made, for reasons which are discussed above, the burden of coming forward with evidence or data regarding inherent properties has not shifted to Applicants.

Even if the interpretation of one of ordinary skill in the art were that a lipid vesicle containing cholesterol sulfate in the membrane layer and NADG encapsulated therein was equivalent to the integral mixture of the present invention, Applicants assert that it would be rebutted by the surprising results of the present invention. The Examiner asserts in the final office action that the Example in the present specification provides no clear and convincing evidence of nonobviousness or unexpected results since it is not a direct comparison between the present invention and the cited prior art references. However, Applicants note that all evidence of nonobviousness must be considered. *In re Soni*, 44 USPQ2d 1684, 1687 (1995). As Applicants have pointed out in previous responses, the two systems are not the same and there is no reason to believe that the integral mixture of the ingredients of the present invention directly in a vehicle would necessitate a comparison with a lipid vesicle as these are two completely different systems and different arrangements of the components. To support this fact, Applicants previously submitted a copy of an article, Bouwstra et al., "Cholesterol sulfate and calcium affect stratum corneum lipid organization over a wide temperature range" Journal of Lipid Research, vol. 40, 2303-3212 (Dec. 1999). In the article, the authors note that reduced levels of cholesterol sulfate contribute to desquamation, thus indicating that the presence of cholesterol sulfate would maintain the integrity of the stratum corneum and prevent desquamation. Therefore, Applicants maintain that one of ordinary skill in the art would expect a combination of cholesterol sulfate and an exfoliant to have no effect on the surface on the skin because while the exfoliant would contribute to desquamation, the cholesterol sulfate would act to prevent desquamation.

To recapitulate, the present invention is based on the finding that two ingredients, the cholesterol sulfate and the exfoliant, although they have opposing activities, when added as a mixture to a

pharmaceutical or cosmetic vehicle, do not neutralize one another's activities, but rather their activity occurs in tandem, and can improve or maintain a healthy skin barrier. As previously mentioned, this benefit cannot even be addressed with the cited references because these two materials form lipid vesicles, and therefore, are not in fact mixed. Rather, they are separated such that one, the cholesterol sulfate, is part of a protective membrane that encases the other, the NADG. The whole point of the lipid vesicles/lamellar systems of the cited references is to protect and prevent the active inside from integrating with anything else. Thus, a comparison of this kind would be futile.

CONCLUSION

The present invention, as amended, is an integral mixture of an exfoliant and a cholesterol sulfate that is not taught or suggested by the cited references describing lipid vesicles having one bilayer containing N-acetyl D-glucosamine, and another bilayer containing cholesterol sulfate as the component are arranged differently. Because none of the cited references alone nor in combination would lead one of ordinary skill in the art to the compositions and methods of the present invention, a *prima facie* case of obviousness has not been established. Applicants request therefore, that the Examiner's rejection under §103 be withdrawn. In view of the arguments presented above in the present submission, the claims are believed to be in condition for allowance, and issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,

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Dorene M. Price (Reg. No. 43,018)
Estee Lauder Companies
155 Pinelawn Road
Suite No. 345 South
Melville, NY 11747
(631) 414-6087